

**REMARKS**

Claims 26-46 are pending in the application.

**I. Nonstatutory Obviousness-Type Double Patenting**

The Examiner rejected Claims 26-27, 29-31, 33-35 and 38-46 as allegedly being unpatentable over Claims 1-2, 8-10, 22-23 and 27 of U.S. Patent No. 6,471,968 (hereinafter "the '968 patent") in view of Tomalia et al., Agnew Chem. Int. Ed. Engl. 29, 138-175 (1990) (Office Action, page 3).

Applicants respectfully disagree.

Nonetheless, without acquiescing to any of the Examiner's arguments and in order to further the prosecution of the present invention, Applicants herein agree to file a terminal disclaimer with regard to the '968 patent. Applicants believe that this renders the Examiner's nonstatutory obviousness-type double patenting rejection moot.

**II. The Claims are Not Obvious**

The Examiner rejected Claims 26-35 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tomalia et al., Agnew Chem. Int. Ed. Engl. 29, 138-175 (1990) (hereinafter "Tomalia et al.") in view of Malik et al. (Proceed. Int'l Symp. Control. Rel. Bioact. Mater., 24: 107-108 (1997) hereinafter "Malik et al.") (Office Action page 5); and Claims 26-27 and 36-37 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Tomalia et al. in view of U.S. Patent No. 5,714,166 (herein after "the '166 patent") (Office Action page 6).

Applicants respectfully disagree.

A *prima facie* case of obviousness requires the Examiner to provide a reference(s) which (a) discloses all of the elements of the claimed invention, (b) suggests or motivates one skilled in the art to combine the claimed elements to produce the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of these three requirements precludes a finding of a *prima facie* case of obviousness and without more entitles Applicants to allowance of the claims in issue.<sup>1</sup>

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<sup>1</sup> See *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Examiner's rejection is improper because the Examiner has failed to cite to references that, individually or in combination, teach each element of the claimed invention, provide a suggestion or motivation to modify or combine the references to generate the claimed invention, or that provide a reasonable expectation of success of generating the claimed invention to one of ordinary skill in the art.

**A) The Claims are Not Obvious over Tomalia et al. in View of Malik et al.**

**1) The Cited References Do Not Teach or Disclose Each Element of the Claimed Invention**

The Examiner alleges that

"Tomalia et al. teach ester-terminated PAMAM (G0-G10), hydroxylated terminated PAMA (G0-G9), ketone terminated PAMAM (-NHCOR for G0-G6), and many more (p. 163-167, also see Table 8 on p.165)." (Office Action page 4).

However, the Examiner fails to cite to a reference within Tomalia that teaches or discloses dendrimer acetylation.

In fact, Tomalia et al. does not teach or disclose dendrimer acetylation.

With regard to Malik et al., the Examiner alleges that:

"It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the chemotherapeutic agent [of Malik et al.], cisplatin into a PAMAM dendrimer with the functional groups as described by Tomalia et al, since Tomalia teaches dendrimer metal complexes." (Office Action page 6, lines 4-7).

However, this allegation fails to supplement the deficiencies of Tomalia et al.

Malik et al. does not teach, describe or suggest a composition comprising an acetylated dendrimer. In fact, the Examiner does not allege that Malik provides such a teaching or suggestion.

Applicants respectfully submit that the Examiner fails to cite to a teaching or discussion of dendrimer acetylation in the cited references because one simply does not exist. Thus, the cited references do not teach or disclose all elements of the present invention. This alone defeats the Examiner's allegation of *prima facie* obviousness.

**2) The Examiner Does Not Provide Objective Evidence Suggesting the Claimed Invention**

Without citing a teaching, discussion or suggestion of an acetylated G5 POPAM or POPAM dendrimer comprising one or more functional groups from the cited references, the Examiner alleges that

"Changing the functional group from a highly positive charged amine terminated dendrimer to a neutral acetyl terminated dendrimer would be an obvious choice by one skilled in the art if one did not want the dendrimer reacting with surrounding negatively charged compounds" (Office Action page 4);

and that "One of ordinary skill in the art would be motivated to obtain a neutral surface that would impart the neutral charge, such as the acetyl group" (Office Action page 7).

These allegations are not factually or legally supportable.<sup>2</sup> Indicative of the lack of obviousness, the Examiner is unable to cite to any objective evidence within the cited references, or from anywhere, that teaches or suggests modifying a dendrimer via acetylation. Instead, looking backwards in time at the presently claimed invention, the Examiner simply puts forth the Examiner's opinion that it would have been an obvious choice to modify a dendrimer via acetylation.

Applicants respectfully submit that, as set forth in 35 U.S.C. §103(a), obviousness is determined at the time the invention was made. Accordingly, "it is...necessary that the decision maker forget what he or she has been taught... about the claimed invention and cast the mind back to the time the invention was made..." See MPEP §2141.01(III). Accordingly, what is allegedly obvious now is not relevant to the obviousness inquiry.<sup>3</sup>

Thus, it is well established that the teaching or suggestion to make the claimed combination must be found in the cited references and not based on applicant's disclosure to establish or "support" a *prima facie* case of obviousness.

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<sup>2</sup> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). See also *In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000)

<sup>3</sup> "Although the suggestion to combine references may flow from the nature of the problem, '[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.'" (internal citation omitted) (quoting *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)); *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992).

Applicants respectfully submit that the Examiner's allegation that "One of ordinary skill in the art would be motivated to obtain a neutral surface that would impart the neutral charge, such as the acetyl group" (Office Action page 7) finds no basis in the cited references or elsewhere. In fact, the Examiner has pointed to no such teaching or suggestion from the cited references but rather has simply opined this to be the case. Thus, the Examiner has failed to cite to objective evidence from the cited references, or from anywhere, that provides one of ordinary skill in the art a teaching or suggestion to make the claimed modification.

In fact, the teachings of the cited references lead one of ordinary skill in the art away from the presently claimed invention.

### **3) The Cited References Teach Away From the Claimed Invention**

According to the MPEP, a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention.<sup>4</sup> Moreover, a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.<sup>5</sup>

As acknowledged by the Examiner, "Tomalia et al teach ester-terminated PAMAM (G0-G10), hydroxylated terminated PAMA (G0-G9), ketone terminated PAMAM (-NHCOR for G0-G6), and many more (p. 163-167, also see Table 8 on p.165)." (Office Action page 4). However, the Examiner fails to acknowledge that the surface reactions disclosed by Tomalia et al., in addition to being "used in various combinations to create stratified dendrimers with differentiated generations possessing different segment lengths, different branch-juncture multiplicities, and varied hydrophobicity[.]"<sup>6</sup> existed for subsequent functionalization of the dendrimer. In other words, the surface reactions disclosed by Tomalia et al. existed for generating dendrimers with reactive groups for conjugation to other moieties. For example, Tomalia et al. disclose surface reactions of a dendrimer that "can be used to produce linear nonbranched dendrimer segments which possess interior OH groups. Since the OH groups do

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<sup>4</sup> See *In re Geisler*, 116F.3d 1465, 1471, 43 USPQ3d 1362, 1366 (Fed. Cir. 1997). MPEP §2144.05(III).

<sup>5</sup> See *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (See MPEP §2141.02).

<sup>6</sup> See Tomalia et al., page 164, right column, fourth sentence of the last paragraph beginning on page 164 and continued on page 165.

not participate in Michael addition reactions, these hydroxylated segments can be subsequently functionalized."<sup>7</sup>

Thus, in stark contrast to the Examiner's allegation that Tomalia et al. disclose or suggest an acetylated dendrimer of the present invention, one of ordinary skill in the art immediately appreciates that Tomalia et al. teach dendrimer surface modifications that increase the dendrimer's ability to react with and/or to be conjugated to other moieties (e.g., surrounding compounds).

Thus, Applicants respectfully submit that various teachings of Tomalia et al. lead one of ordinary skill in the art away from an acetylated dendrimer defined by Claims 26-46 of the instant application.

**4) The Cited References Provide No Reasonable Expectation of Success for Generating the Claimed Invention**

As described above, in addition to citing to references that fail to teach or suggest each element of the presently claimed invention, the examiner also made an improper hindsight analysis. In doing so, the Examiner failed to acknowledge or to examine the state of the art at the time of the invention. For example, the Examiner ignores determining whether one of ordinary skill in the art **at the time of the invention** would have been motivated to make such a modification or whether such a modification would have been expected to generate a functional dendrimer. In particular, the Examiner fails to acknowledge or to discuss how the allegedly obvious acetylation would impact, alter or change dendrimer reactivity necessary for conjugation of the dendrimer to one or more functional groups (e.g., fluorescein isothiocyanate and/or folic acid), or whether acetylation of a dendrimer would even be possible post conjugation of the dendrimer to a functional group (e.g., whether any reactive amino termini remained post conjugation). Furthermore, the Examiner fails to address whether one of ordinary skill in the art at the time of the invention would have expected acetylation of a dendrimer to produce a functional, soluble dendrimer.

Tomalia et al. in fact teach the unpredictable nature of dendrimer chemistry. For example, Tomalia et al. describe that

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<sup>7</sup> See Tomalia et al., page 165, left column, lines 1-5.

"dendrimers can be controlled by appropriate choices of  $N_c$ ,  $N_b$  and branch-segment lengths  $l$ , as well as the flexibility and shapes of the branch segments. A qualitative overview of how  $N_c$  and  $N_b$  may affect interior topology is provided by the two-dimensional projections shown in Figure 45. Because of the variety of possible heteroatoms or functional groups, it is easy to conceptualize many new endo-receptor microenvironments, which would resemble multiarmed entities described by Vogtle and Weber,<sup>[119]</sup> Suckling,<sup>[120]</sup> and Menger<sup>[121]</sup> or pseudo-macrocyclic (cryptate-like) prototypes.<sup>[9, 13, 34-36]</sup> **Very little is known about these dendrimer properties** although it has been noted that ester-terminated PAMAM dendrimers form deep blue complexes with  $\text{CuSO}_4$  solutions, whereas  $\text{NH}_2$ -terminated homologues produce deep purple solutions.<sup>[62]</sup> The well-known coordination properties of the amide bond, which lead to the formation of metal-ion complexes,<sup>[122]</sup> **should make this a very rich area for further investigation.**<sup>8</sup>

Thus, the Examiner's broad, hindsight allegation that it would have been an obvious choice by one skilled in the art to change the functional group from a reactive and highly positive charged amine terminated dendrimer to a neutral acetyl terminated dendrimer if one did not want the dendrimer reacting with surrounding negatively charged compounds (Office Action page 4) not only fails to cite to any objective evidence supporting this allegation, but also fails to provide a reasonable expectation of success for generating the claimed invention to one of ordinary skill in the art. In fact, as cited above, Tomalia et al. teach the unpredictable nature of dendrimer chemistry (e.g., surface chemistry and solubility).

Thus, the Examiner has failed to cite objective evidence from the cited references, or from anywhere, that modification of a dendrimer via acetylation would generate a functional dendrimer (e.g., that an acetylated dendrimer would in fact be useful (e.g., soluble)) or that addresses the state of the art at the time of the invention (e.g., the importance of a dendrimer possessing reactive amino termini (e.g., for conjugation to a therapeutic agent and other functional groups)).

Applicants submit, for the sake of argument, that even if the references provide a generalized teaching to try to modify the surface chemistry of a dendrimer using acetylation, that this is nothing more than an invitation to experiment and does not render obvious Applicants' invention.

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<sup>8</sup> See Tomalia et al., page 163, last paragraph of right column continued on top of left column of page 164, emphasis added.

The courts have clearly stated that the "obvious to try" test is not the test prescribed by the patent statutes.

[A]pplication of the "obvious to try" test would often deny patent protection to inventions growing out of well-planned research which is, of course, guided into those areas in which success is deemed most likely. These are, perhaps, the obvious areas to try. But resulting inventions are not necessarily obvious. Serendipity is not a prerequisite to patentability. Our view is that "obvious to try" is not a sufficiently discriminatory test.<sup>9</sup>

Thus, "obvious to experiment" is not the standard for obviousness.<sup>10</sup> The Federal Circuit has made very clear that one must determine whether "the prior art would have suggested to one of ordinary skill in the art that this process **should** be carried out and **would** have a reasonable likelihood of success, viewed in light of the prior art."<sup>11</sup>

There is no reasonable expectation of success because, as described above, there was no way to predict whether modification of a dendrimer via acetylation would generate a functional dendrimer (e.g., that an acetylated dendrimer would in fact be useful (e.g., soluble)). Applicants respectfully submit that the Examiner has improperly applied an "obvious to experiment" standard.

Thus, the Examiner has failed to cite to objective evidence rendering *prima facie* obvious a composition comprising an acetylated generation 5 (G5) polyamideamine (PAMAM) or polypropylamine (POPAM) dendrimer wherein the acetylated dendrimer comprises one or more functional groups, wherein at least one of the functional groups comprises a therapeutic agent.

Accordingly, the claims are not rendered obvious over Tomalia et al. in view of Malik et al. Applicants respectfully request the Examiner withdraw rejection of Claims 26-35 under 35 U.S.C. § 103(a).

**B) The Claims are Not Obvious over Tomalia et al. in View of the '166 Patent**

With regard to the '166 patent, the Examiner alleges that

"One of ordinary skill in the art would be motivated to obtain a neutral surface that would be less reactive with biological compounds to look for a functional group that would impart the neutral charge, such as the acetyl group. It would have been *prima facie*

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<sup>9</sup> See *In re Lindell* 155 U.S.P.Q. 521, 523 (CCPA 1967, citing *In re Tomlinson*, 150 U.S.P.Q. 623 (1966).

<sup>10</sup> *In re Dow Chemical*, 5 USPQ2d 1529, at 1532 (Fed. Cir. 1988).

<sup>11</sup> *Id.* at 1531 (Emphasis added)

obvious to one of ordinary skill in the art that since PAMAM dendrimers are non-toxic and useful for specific delivery of imaging and targeting agents, to look to the teachings '166 (the conjugation of PAMAM dendrimers to targeting and imaging agents, specifically fluorescein isothiocyanate) in conjunction with Tomalia et al to obtain an acetylated PAMAM dendrimer for use in targeting and imaging in vitro." (Office Action, page 7, lines 6-14).

This allegation is not factually or legally supportable.

Tomalia et al. does not teach, describe or suggest a composition comprising an acetylated dendrimer. Similarly, the '166 patent does not teach, describe or suggest a composition comprising an acetylated dendrimer. Accordingly, the cited references do not render the presently claimed invention *prima facie* obvious.

Without reference to objective evidence suggesting dendrimer acetylation, the Examiner alleges that "One of ordinary skill in the art would be motivated to obtain a neutral surface that would be less reactive with biological compounds to look for a functional group that would impart the neutral charge, such as the acetyl." Thus, the Examiner alleges, without putting forth any objective evidence, that the state of the art at the time of the invention was such that one of ordinary skill in the art would have been motivated to generate an acetylated dendrimer.

As described above, in addition to being impermissible hindsight reconstruction of the claimed invention, this allegation fails to consider the state of the art at the time of the present invention (e.g., the importance of a dendrimer possessing reactive amino termini (e.g., for conjugation to a therapeutic agent and other functional groups)). The allegation also fails to cite objective evidence providing the motivation to modify a dendrimer via acetylation and whether there would have been a reasonable expectation of success of generating a functional (e.g., soluble and/or stable), acetylated dendrimer. Furthermore, as described above, the cited references teach away from the claimed invention.

Accordingly, the claims are not rendered *prima facie* obvious in view of the cited references. Applicants respectfully request the Examiner withdraw rejection of Claims 26-35 under 35 U.S.C. § 103(a).

### **CONCLUSION**

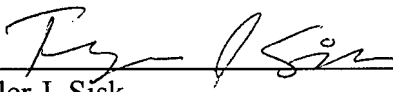
For the reasons set forth above, it is respectfully submitted that Applicants have addressed all grounds for rejection and Applicants' claims should be passed to allowance.



Reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned collect at (608-218-6900).

Respectfully submitted,

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